EUROPEAN PATENT OFFICE
INTERNATIONAL PRELIMINARY EXAMINING
AND SEARCHING AUTHORITY

Applicant: Emory University
International Appln. No. PCT/US2005/001710
International Filing Date: 20 January 2005

Title: COMPOSITIONS AND METHODS OF USE FOR TYROSINE KINASE INHIBITORS TO TREAT PATHOGENIC INFECTION

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AMENDMENTS UNDER ARTICLE 34 AND
RESPONSE TO
FIRST WRITTEN OPINION ON PRELIMINARY EXAMINATION

Sir:

This is in response to the Written Opinion dated 26 October 2005, from the International Searching Authority ("ISA"). Applicant has amended this application as described more fully below. Accordingly, kindly substitute the enclosed replacement sheets for the corresponding original sheets in the above identified application.

Explanation of Differences Between the Original Sheets and the Replacement Sheets

Applicants submit replacement pages 1 and 1A to replace original page 1 of the above-identified application. These sheets contain the same text as original page one except that a government support clause has been added under the heading "FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT" stipulating that the U.S. government has certain rights in the invention.

Applicants also submit new claims 1 to 26 and cancel original claims 1 to 25. Old claim 2 has been amended to include the word "also" in order to clarify that the claimed method utilizes tyrosine kinase inhibitors that are also useful for treating

or preventing a form of cancer comprising chronic myelogenous leukemia (see new claim 2). In addition, the new claims reflect a correction of the numbering of the old claims wherein two claims had been listed as "claim 24." No new matter has been added by way of these claim amendments. To make these changes, new pages 49 to 55 are submitted in replacement of original pages 49 to 55 of the above-identified application.

REMARKS

In the Written Opinion at section V, subsection 1, the Examiner objects to claims 1-6, 10, 12-15, 18, 20, and 23-25 as not meeting the requirements of Article 33(2) PCT. In addition, at section V, subsection 2 of the Written Opinion, the Examiner objects to claims 1-15 as not meeting the requirements of Article 33(3) PCT. While Applicants disagree with Examiner's conclusions, these matters will be addressed during national phase.

CONCLUSION

Applicants have amended the specification and claims of the present application and have reserved the right to address substantive issues relating to the conclusions drawn by the Examiner in the Written Opinion during national phase.

Respectfully submitted,

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Attorney Docket No. 07157/287376

COMPOSITIONS AND METHODS OF USE FOR TYROSINE KINASE INHIBITORS TO TREAT PATHOGENIC INFECTION

FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT

This invention was made with government support under AI056067 awarded by the National Institutes of Health. The United States Government has certain rights in the invention.

FIELD OF THE INVENTION

The invention relates to compositions and methods for using tyrosine kinase inhibitors to treat pathogenic infection associated with or caused by host-cell interactions involving tyrosine kinases. In particular, the present invention relates to the use of Abl-family tyrosine kinase inhibitors to treat infection from microbial pathogens such as bacteria and viruses.

BACKGROUND OF THE INVENTION

The last several decades have witnessed an onslaught of deadly pathogens around the globe. A broad array of human pathogens exists, including various microbes such as bacteria, protozoa, viruses, algae, and fungi. The innate capacity to respond to selective pressures has driven the evolution of microbes and enabled them to adapt to complex and variable environments. It is perhaps no surprise, then, that infectious microbes have readily evolved mechanisms to evade our attempts to destroy them with synthetic or natural anti-microbial compounds.

The fact that microbes develop resistance at a rate that far exceeds development of new therapeutics arguably poses the single most serious public

health threat in this century in both developing and developed nations. There is no denying that anti-microbial strategies have met with spectacular success over the last century. For example, antibacterial and antiviral drugs directed at targets within the pathogen have been used to save countless lives. But it is becoming increasingly evident that such success is not sustainable. To counter these drugs, bacteria and viral pathogens have evolved sophisticated mechanisms to inactivate these compounds. Examples include the pan-drug resistant strains of *Staphylococcus aureus, Klebsiella pneumonia*, and *Pseudomonas aerginosa*, and *Mycobacterium tuberculosis* (TB) among bacteria and human immunodeficiency virus (HIV) among viruses.

CLAIMS

What is claimed is:

1. A method for preventing or treating a bacterial infection or a viral infection comprising administering a therapeutically effective amount of a tyrosine kinase inhibitor to a subject in need thereof.

2. The method of claim 1, wherein said tyrosine kinase inhibitor inhibits actin motility and viral release and wherein said tyrosine kinase inhibitor is also useful for treating or preventing a form of cancer comprising chronic myelogenous leukemia.

3. The method of claim 1, wherein said tyrosine kinase inhibitor inhibits at least one Abl-family tyrosine kinase or Src-family tyrosine kinase.

4. The method of claim 3, wherein said Abl-family tyrosine kinase inhibitor is imatinib mesylate or a pharmaceutically acceptable salt, enantiomer, analog, ester, amide, prodrug, metabolite, or derivative of imatinib mesylate.

5. The method of claim 4, wherein said derivative of imatinib mesylate is STI-X.

6. The method of claim 3, wherein said Abl-family tyrosine kinase inhibitor is a pyrido[2,3-d]pyrimidine.

7. The method of claim 6, wherein said pyrido[2,3-d]pyrimidine is PD173955, PD173952, PD173958, PD173956, PD166326, SKI DV1-10, PD180970; SKI DV2-43, SKI DV2-47, SKI DV1-28, SKI DV2-45, SKI DV2-35, SKI DV2-33, SKI DV2-89, SKI DV-M017, SKI DV-M016, SKI DV2-43, SKI DV2-53, SKI DV2-71, or SKI DV2-87.

8. The method of claim 7, wherein said pyrido[2,3-d]pyrimidine is PD173952 or PD166326.

9. The method of claim 1, wherein said tyrosine kinase inhibitor is ZD-6474, PTK-787/ZK-224584, CP-547632, BMS354825, SU11248, SU011248, gefitinib, or erlotinib.

10. The method of claim 1, wherein said tyrosine kinase inhibitor is administered orally, nasally, buccally, sublingually, intravenously, transmucosally, rectally, topically, transdermally, subcutaneously, by inhalation, or intrathecally.

11. The method of claim 1, wherein said viral infection is caused by a Vaccinia virus, a variola virus, a JC, a BK, a herpes, or a human immunodeficiency virus.

12. The method of claim 1, wherein said bacterial infection is caused by *Escherichia coli*, *Helicobacter pylori*, *Listeria monocytogenes*, *Salmonella typhimurium*, *Shigella Flexneri*, or *Mycobacterium tuberculosis*.

13. A method for administering a tyrosine kinase inhibitor to a subject for the prevention or treatment of a viral infection caused by a Vaccinia virus, a variola virus, a polyoma virus, a Herpes virus, a cytomegalovirus (CMV), or a human immunodeficiency virus.

14. The method of claim 13, wherein said tyrosine kinase inhibitor is an Abl-family tyrosine kinase inhibitor.

15. The method of claim 14, wherein said Abl-family tyrosine kinase inhibitor is imatinib mesylate, STI-X, or a pyrido[2,3-d]pyrimidine.

16. The method of claim 15, wherein said pyrido[2,3-d]pyrimidine is PD173955, PD173952, PD173958, PD173956, PD166326, SKI DV1-10, PD180970; SKI DV2-43, SKI DV2-47, SKI DV1-28, SKI DV2-45, SKI DV2-35, SKI DV2-33, SKI DV2-89, SKI DV-M017, SKI DV-M016, SKI DV2-43, SKI DV2-53, SKI DV2-71, or SKI DV2-87.

17. The method of claim 14, wherein said tyrosine kinase inhibitor is ZD-6474, PTK-787/ZK-224584, CP-547632, BMS354825, SU11248, SU011248, gefitinib, or erlotinib.

18. A method for administering a tyrosine kinase inhibitor to a subject for the prevention or treatment of a bacterial infection caused by *Escherichia coli*, *Helicobacter pylori*, *Listeria monocytogenes*, *Salmonella typhimurium*, *Shigella Flexneri*, or *Mycobacterium tuberculosis*.

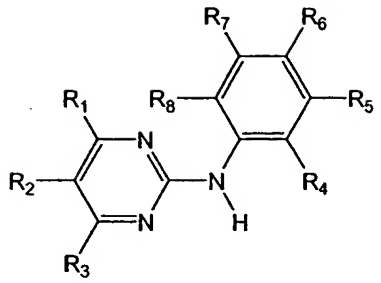
19. The method of claim 18, wherein wherein said tyrosine kinase inhibitor inhibits an Abl-family tyrosine kinase.

20. The method of claim 19, wherein said Abl-family tyrosine kinase inhibitor is imatinib mesylate, STI-X, or a pyrido[2,3-d]pyrimidine.

21. The method of claim 20, wherein said pyrido[2,3-d]pyrimidine is PD173955, PD173952, PD173958, PD173956, PD166326, SKI DV1-10, PD180970; SKI DV2-43, SKI DV2-47, SKI DV1-28, SKI DV2-45, SKI DV2-35, SKI DV2-33, SKI DV2-89, SKI DV-M017, SKI DV-M016, SKI DV2-43, SKI DV2-53, SKI DV2-71, or SKI DV2-87.

22. The method of claim 18, wherein said tyrosine kinase inhibitor is ZD-6474, PTK-787/ZK-224584, CP-547632, BMS354825, SU11248, SU011248, gefitinib, or erlotinib.

23. A method for preventing or treating a bacterial infection or a viral infection comprising administering a therapeutically effective amount of a tyrosine kinase inhibitor to a subject in need thereof, wherein said tyrosine kinase inhibitor comprises a compound according to the formula:



wherein:

R_1 is 4-pyrazinyl, 1-methyl-1H-pyrrolyl, amino-, or amino-lower alkyl-substituted phenyl wherein the amino group in each case is free, alkylated, or acylated, 1H-indolyl or 1H-imidazolyl bonded at a five-membered ring carbon atom, or unsubstituted or lower alkyl-substituted pyridyl bonded at a ring carbon atom and unsubstituted or substituted at the nitrogen atom by oxygen;

R_2 and R_3 are each independently of the other hydrogen or lower alkyl, one or two of the radicals R_4, R_5, R_6, R_7, and R_8 are each nitro, fluoro-substituted lower alkoxy or a radical of the formula

$$-N(R_9)-C(=X)-(Y)_n-R_{10};$$

wherein:

R_9 is hydrogen or lower alkyl;

X is oxo, thio, imino, N-lower alkyl-imino, hydroximino, or O-lower alkyl-hydroximino;

Y is oxygen or the group NH,

n is 0 or 1; and

R_{10} is an aliphatic radical having at least 5 carbon atoms, or an aromatic, aromatic-aliphatic, cycloaliphatic, cycloaliphatic-aliphatic, heterocyclic, or hetero-cyclicaliphatic radical;

and the remaining radicals R_4, R_5, R_6, R_7, and R_8 are each independently of the others hydrogen, lower alkyl that is unsubstituted or substituted by free or alkylated amino, piperazinyl, piperidinyl, pyrrolidinyl or by morpholinyl, or lower alkanoyl, trifluoromethyl, free, etherified, or esterified hydroxy, free, alkylated or acylated amino or free or esterified carboxy;

or a pharmaceutically acceptable salt, enantiomer, analog, ester, amide, prodrug, metabolite, or derivative thereof.

24. The method according to claim 23, wherein said tyrosine kinase inhibitor comprises a compound according to the formula of claim 23 wherein:

R_1 is 4-pyrazinyl, 1-methyl-1H-pyrrolyl, amino-, or amino-lower alkyl-substituted phenyl wherein the amino group in each case is free, alkylated by one or two lower alkyl radicals or acylated by lower alkanoyl or by benzoyl, 1H-indolyl or 1H-imidazolyl bonded at a five-membered ring carbon atom, or unsubstituted or lower alkyl-substituted pyridyl bonded at a ring carbon atom and unsubstituted or substituted at the nitrogen atom by oxygen;

R_2 and R_3 are each independently of the other hydrogen or lower alkyl, one or two of the radicals R_4, R_5, R_6, R_7, and R_8 are each nitro, fluoro-substituted lower alkoxy or a radical of the formula

$$-N(R_9)-C(=X)-(Y)_n-R_{10};$$

wherein:

R_9 is hydrogen or lower alkyl;

X is oxo, thio, imino, N-lower alkyl-imino, hydroximino, or O-lower alkyl-hydroximino;

Y is oxygen or the group NH;

n is 0 or 1; and

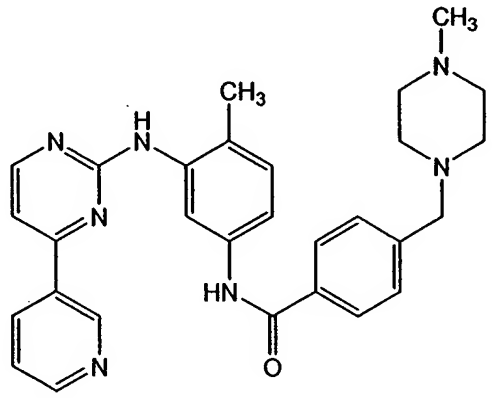
R_{10} is an aliphatic hydrocarbon radical having 5-22 carbon atoms, a phenyl or naphthyl radical each of which is unsubstituted or substituted by cyano, lower alkyl, hydroxyl-lower alkyl, amino-lower alkyl, (4-methyl-piperazinyl)-lower alkyl, trifluoromethyl, hydroxy, lower alkoxy, lower alkanoyloxy, halogen, amino, lower alkylamino, di-lower alkylamino, lower alkanoylamino, benzolylamino, carboxy or by lower alkoxycarbonyl, or phenyl-lower alkyl wherein the phenyl radical is unsubstituted or substituted as indicated above, a cycloalkyl or cycloalkenyl radical having up to 30 carbon atoms, cycloalkyl-lower alkyl or cycloalkenyl-lower alkyl each having up to 30 carbon atoms in the cycloalkyl or cycloalkenyl moiety, a monocyclic radical having 5 or 6 ring members and 1-3 ring hetero atoms selected from nitrogen, oxygen, and sulfur, to which radical one or two benzene radicals may be fused, or lower alkyl substituted by such a monocyclic radical;

and the remaining radicals R_4, R_5, R_6, R_7, and R_8 are each independently of the others hydrogen, lower alkyl that is unsubstituted or substituted by amino, lower alkylamino, di-lower alkylamino, piperazinyl, piperidinyl, pyrrolidinyl, or by

morpholinyl, or lower alkanoyl, trifluoromethyl, hydroxy, lower alkoxy, lower alkanoyloxy, halogen, amino, lower alkylamino, di-lower alkylamino, lower alkanoylamino, benzoylamino, carboxy, or lower alkoxycarbonyl;

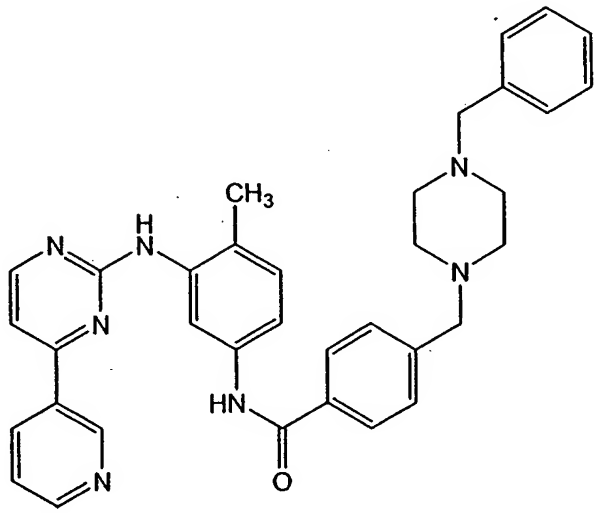
or a pharmaceutically acceptable salt, enantiomer, analog, ester, amide, prodrug, metabolite, or derivative thereof.

25. A method for preventing or treating a bacterial infection or a viral infection comprising administering a therapeutically effective amount of a tyrosine kinase inhibitor to a subject in need thereof, wherein said tyrosine kinase inhibitor comprises a compound according to the formula:



or a pharmaceutically acceptable salt, enantiomer, analog, ester, amide, prodrug, metabolite, or derivative thereof.

26. The method according to claim 25, wherein said tyrosine kinase inhibitor comprises a derivative according to the formula:



or a pharmaceutically acceptable salt, enantiomer, analog, ester, amide, prodrug, metabolite, or derivative thereof.